

*DB=PGPB; PLUR=YES; OP=ADJ*

L11 (fish adj oil) same (antibod\$ or immunoglobulin\$ or immunosuppressive\$ or rapamycin\$) 417 L11

*DB=DWPI; PLUR=YES; OP=ADJ*

L10 (("DE 3781686G")!.ABPN1,NRPN.) .p22-p52. 1 L10

*DB=EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ*

L9 (fish adj oil) same (antibod\$ or immunoglobulin\$ or immunosuppressive\$ or rapamycin\$) 4 L9

*DB=USPT; PLUR=YES; OP=ADJ*

L8 L7 same (antibod\$ or immunoglobulin\$ or immunosuppressive\$ or rapamycin\$) 30 L8

L7 (fish adj oil) same (pharmaceutical or therapeutic) same (composition\$) 100 L7

L6 (rapamycin\$) and (kit\$) same (pharmaceutical or therap\$ or treat\$) same (immunosuppressiv\$) 22 L6

L5 (rapamycin\$) and (kit\$) same (pharmaceutical or therap\$ or treat\$) same (antibod\$) 115 L5

L4 (rapamycin\$) and (kit\$) same (pharmaceutical or therap\$ or treat\$) 516 L4

*DB=PGPB; PLUR=YES; OP=ADJ*

L3 11 51 L3

*DB=USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ*

L2 L1 25 L2

*DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ*

L1 (rapamycin\$) same (kit\$) same (pharmaceutical or therap\$ or treat\$) 76 L1

END OF SEARCH HISTORY



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(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0202650 A1****Gribben et al.**(43) **Pub. Date: Oct. 14, 2004**(54) **METHODS OF INHIBITING T CELL PROLIFERATION OR IL-2 ACCUMULATION WITH CTLA-4 SPECIFIC ANTIBODIES**(52) **U.S. Cl. .... 424/131.1; 424/144.1**(76) **Inventors:** John G. Gribben, Brookline, MA (US); Gordon J. Freeman, Brookline, MA (US); Lee M. Nadler, Newton, MA (US); Paul D. Rennert, Holliston, MA (US); Cindy L. Jellis, Londonderry, NH (US); Edward Greenfield, Randolph, MA (US); Gary S. Gray, Brookline, MA (US)**Correspondence Address:**  
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**BOSTON, MA 02109 (US)**(21) **Appl. No.: 10/732,847**(22) **Filed: Dec. 9, 2003****Related U.S. Application Data**(62) **Division of application No. 08/253,783, filed on Jun. 3, 1994, now Pat. No. 6,719,972.****Publication Classification**(51) **Int. Cl.<sup>7</sup> ..... A61K 39/395**(57) **ABSTRACT**

Isolated ligands which bind a molecule expressed on the surface of T cells and induce antigen specific apoptosis in activated T cells are disclosed. Preferably, the T cell surface molecule is CTLA4 and the ligand is a monoclonal anti-CTLA4 antibody that binds to an epitope of CTLA4 distinct from the binding sites of B7-1 and B7-2. Upon binding of the antibody to CTLA4 on an activated T cell, in the presence of an antigenic signal, antigen specific apoptosis is induced. The invention also describes a novel natural CTLA4 ligand, distinct from B7-1 and B7-2, which mediates induction of apoptosis. Pharmaceutical compositions of anti-CTLA4 antibodies or other isolated CTLA4 ligands which can be administered to subjects to induce T cell apoptosis, thereby clonally deleting antigen specific T cells, such as alloreactive T cells in transplantation situations or autoreactive T cells in autoimmune disorders, are also disclosed. Methods for inducing T cell apoptosis in vitro with an anti-CTLA4 antibody or other ligand of the invention together with an antigen specific signal are also disclosed, e.g., for use in purging alloreactive T cells from donor bone marrow prior to bone marrow transplantation to inhibit graft versus host disease.

